Proposed Re-evaluation Decision PRVD2017-06

Amitraz

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Executive Summary

Health Canada's Pest Management Regulatory Agency (PMRA)

Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency before they can be imported, sold, or used in Canada. Pesticides must go through rigorous science-based assessments before being approved for sale in Canada.

All registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environment safety standards and continue to have value. This may happen even sooner if there have been changes in the required information or to the risk assessment methodology. Re-evaluations may result in:

- changes to how products are used;
- changes to product labels to meet current health and environmental standards; or,
- removing products from the market to prevent future harm to health or the environment.

Re-evaluation of Amitraz for Pet Collar Use

Amitraz is an acaricide/insecticide registered to control American and brown dog ticks on dogs which are older than 12 weeks of age and with a neck size of up to 62 cm, in a slow release pet collar.

When conducting the re-evaluation of amitraz for pet collar use, the PMRA reviewed scientific information provided by pesticide manufacturers, as well as published scientific information. For the human health assessment, the following exposure scenarios were examined: exposure when applying the collar and postapplication exposure from coming into contact with the pesticide after the collar has been applied. Due to the nature of this use (that is, pet collar use), a dietary and environmental assessment were not required.

Amitraz is also registered for control of Varroa mite in honey bee colonies. However, as this use was registered in 2012, the risk assessment for this use in honey bee colonies is considered up to date and, thus, is not considered in this re-evaluation.

Key Findings

The human health risk assessment found that there are risks of concern from postapplication exposure following contact with dogs wearing amitraz-impregnated pet collars. Therefore, the cancellation of the use of amitraz in pet collars is proposed at this time.

Next Steps

The proposed re-evaluation decision is now open for public consultation for 90 days from the date of this publication. PMRA is inviting the public to submit comments on the proposed re-evaluation decision for amitraz for use in pet collars, including proposals that may refine the risk assessment and risk management. Once PMRA considers the comments and any information that are received during the public consultation period, it will publish a final decision.

Overview

What is the Proposed Re-evaluation Decision for Amitraz Used in Pet Collars?

The evaluation determined that under the current conditions of use, the human health risks for pet collars containing amitraz do not meet current safety standards. Therefore, the PMRA is proposing to cancel the use of amitraz in pet collars.

Before making a final re-evaluation decision on the use of amitraz in pet collars, the PMRA will accept and consider written comments on this proposal received up to 90 days from the date of this publication. Please forward all comments to Publications (see contact information on the cover page of this document). The PMRA will consider any additional data/information submitted during the consultation period in the final decision.

What Does Health Canada Consider When Making a Re-evaluation Decision?

Under the *Pest Control Products Act*, all registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environmental safety standards and continue to have value. The re-evaluation considers data from pesticide manufacturers, published scientific reports, information from other regulatory agencies and other available, relevant information. To reach its decisions, the PMRA applies internationally accepted hazard and risk assessment methods and modern risk management approaches and policies.

For more information on how the PMRA regulates pesticides, as well as the assessment process, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Amitraz?

Amitraz is an acaricide/insecticide currently registered for control of American and brown dog ticks on dogs that are older than 12 weeks of age and with a neck size of up to 62 cm, in a slow release pet collar. It is also registered for the control of Varroa mite in honey bee colonies.

Health Considerations

Can Approved Uses of Amitraz in Pet Collars Affect Human Health?

Risk concerns were identified for the product Preventic Tick Collar for Dogs, containing amitraz, when used according to label directions.

Potential exposure to amitraz may occur when handling and applying this collar, or when coming into contact with dogs wearing the collar. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human

population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using pesticide products according to label directions.

In laboratory animals, the acute oral toxicity of the active ingredient amitraz varied widely among species, ranging from low to high toxicity. Amitraz was slightly acutely toxic via the dermal route, of low toxicity via the inhalation route, minimally irritating to the eyes and skin, and caused an allergic skin reaction. Consequently, following consultation on the proposed decision, if amitraz is deemed acceptable for continued registration in dog collars, the following signal words and hazard statements "DANGER POISON" and "POTENTIAL SKIN SENSITIZER" would be required on the label for this active ingredient.

Preventic Tick Collar for Dogs was of low acute toxicity via the oral and dermal routes, non-irritating to the skin, and did not cause an allergic skin reaction in laboratory animals. Based on the physical form of the product, which is a plastic collar impregnated with amitraz, it is not considered to pose an acute inhalation or an eye irritation hazard. With regards to safety to dogs wearing Preventic Tick Collar for Dogs, the level of concern was low on the basis of an overall assessment, which included a study in dogs wearing collars under conditions that simulated exaggerated exposure to amitraz.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of amitraz to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoint used for risk assessment consisted of effects on the nervous system. There was evidence of sensitivity of the young animal compared to adult animals in the available studies. Information was lacking to adequately assess effects on the nervous system of the young. The risk assessment takes the above noted information into account in determining the allowable level of human exposure to amitraz.

Risks in Residential and Other Non-Occupational Environments

Residential risks of concern were identified for use of the Preventic Tick Collar for Dogs.

Exposure to amitraz can occur when adults handle the Preventic Tick Collar for Dogs and come in direct contact with amitraz residues on the skin. Adults, youth, and children can come in direct contact with amitraz residues on the skin when contacting treated pets. In addition, children can ingest residues by hand-to-mouth activity after contacting treated dogs.

Concern was identified for adults, youth, and children who come into contact with dogs wearing the Preventic Tick Collar for Dogs.

Environmental Considerations

The use of amitraz in dog collars does not pose a risk to the environment as environmental exposure is expected to be negligible.

Value Considerations

Amitraz for use in pest collars is registered to control American and brown dog ticks on dogs. Many ticks are known as vector-borne disease and products, such as pet collars, are one of the ways to help protect dogs from ticks. In addition, veterinary drugs are also available for control of ticks on dogs.

Proposed Measures to Minimize Risk

The PMRA has assessed the available information and concluded that the use of amitraz in pet collars and the associated end-use product used in accordance with the label poses potential risks of concern to human health. Specifically, potential health risk concerns were identified from postapplication exposure to amitraz. Therefore, the PMRA is proposing to cancel the use of amitraz in pet collars in Canada.

What Additional Scientific Information Is Requested?

As the PMRA is proposing cancellation of pet collar uses of amitraz, no additional data will be required.

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (exposure or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments.

Before making a final re-evaluation decision on amitraz, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[1] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

[1] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

Amitraz is under re-evaluation in Canada as described by the Pest Management Regulatory Agency (PMRA) in the 22 November 2011 Re-evaluation Note REV2011-04, *Amitraz*. The purpose of this re-evaluation is to review existing information on the active ingredient, amitraz for use in pet collars, and the domestic class end-use product to ensure that risk assessments meet current standards.

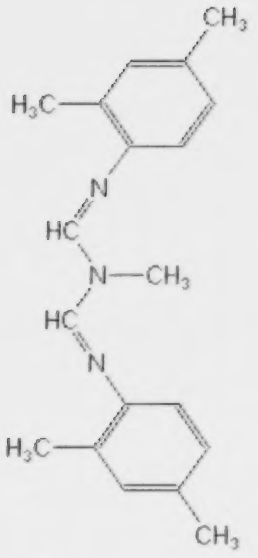
Following the re-evaluation announcement for amitraz, the registrant of the technical grade active ingredient, indicated continued support for registered pet collar uses. Amitraz is an acaricide/insecticide, resistance management Mode of Action (MoA) 19, which acts by interacting with octopamine receptors in the tick nervous system to control American and brown dog ticks on dogs. Currently registered products for pet collar use containing amitraz are listed in Appendix I, Table 1.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		amitraz
Function		insecticide
Chemical Family		formamidine
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	*N,N'*-[(methylimino)dimethylidyne]di-2,4-xylidine
2	**Chemical Abstracts Service (CAS)**	*N'*-(2,4-dimethylphenyl)-*N*-[[(2,4-dimethylphenyl)imino]methyl]-*N*-methylmethanimidamide
CAS Registry Number		33089-61-1
Molecular Formula		$C_{19}H_{23}N_3$

Structural Formula



Molecular Weight	293.4
Purity of the Technical Grade Active Ingredient	97.0% minimum
Registration Number	23485

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	0.34 mPa
Ultraviolet (UV) / visible spectrum	λ_{max} = 290 nm; not expected to absorb >300 nm
Solubility in water at 20°C	<0.1 mg/L
n-Octanol/water partition coefficient at 25°C	Log K_{ow} = 5.5
Dissociation constant	pKa = 4.2

2.3 Description of Registered Amitraz Uses in Pet Collars

As of 3 May 2017, one technical grade active ingredient and one domestic class end-use product were registered in Canada for use in dog collars (Appendix I, Table 1). All uses supported by the registrants at the time of re-evaluation initiation were considered in the risk assessments of amitraz. The use of amitraz in pet collars is to control American and brown dog ticks and belongs to the use-site category 24: companion animals.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A brief summary of the amitraz toxicological database was provided in Evaluation Report ERC2013-04, Amitraz. This summary was based on previous PMRA reviews as well as readily available published scientific literature. The re-evaluation of amitraz resulted in the requirement for information to further characterize the toxicity of amitraz. Although reproductive toxicity studies and non-rodent developmental toxicity studies were available, some were found to have deficiencies and/or did not meet current standards for toxicity testing. In addition, information to assess neurotoxicity from acute and repeated dosing as well as developmental neurotoxicity was not available for amitraz. Consistent with other regulatory authorities, the PMRA applies factors to account for various sources of uncertainty and variability within a toxicology database. The term "uncertainty factor" is used to denote factors associated with interspecies extrapolation, intraspecies variation, extrapolation from a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL) where no NOAEL is available, extrapolation for duration of dosing and database deficiencies. Based on the information available and the corresponding completeness of the data, a 10-fold database uncertainty factor was applied in previous human health risk assessments for amitraz.

Additional information has now been provided to the PMRA. An acute oral neurotoxicity study conducted via gavage and a 90-day dietary neurotoxicity study, both conducted in rats, were submitted. A request to waive the requirement for a non-rodent developmental toxicity study was accepted. Finally, an extended one-generation reproductive toxicity study (EOGRTS) conducted in rats was provided, in which parental animals and their offspring were dosed with amitraz via gavage. In addition to an extensive evaluation of reproductive parameters, the EOGRTS included a screening assessment of developmental neurotoxicity. These data, along with information from the published scientific literature, were incorporated into the overall assessment of the amitraz toxicological database.

In toxicokinetic studies, ^{14}C-amitraz was rapidly absorbed following a single oral dose. Peak levels of radioactivity were detected in the blood of dogs and the urine of rats within 8 hours of dosing. The excretion of amitraz-derived radioactivity by rats, mice, baboons, and humans was also rapid following the administration of a single oral dose, and occurred predominantly via the urine, accounting for 65% to 85% of the administered dose. No significant differences were evident among species or between sexes in terms of percentage excreted in urine. In all species, 55% to 74% of the administered dose was excreted in the urine within the first 24 hours after dosing. Additionally, in mice, dietary pre-treatment with non-radiolabelled amitraz for three weeks did not affect urinary or fecal elimination rates of radioactivity following administration of a single oral dose of ^{14}C-amitraz. The liver, adrenal gland, and/or eyes contained the highest tissue radioactivity levels in rats, mice, and baboons.

In all species tested, amitraz was almost completely metabolized. Conjugates of BTS 28369, which were converted to the free acid upon hydrolysis, were found to be the major urinary metabolites. Other urinary metabolites that occurred in all species at levels of 1% to 6% each included BTS 24868, BTS 27919, BTS 39098, BTS 31158, and BTS 27271. Reaction products formed in gastric juice collected from a dog given a single oral dose of ^{14}C-amitraz included BTS

24868, BTS 27271, and BTS 27919. Unchanged amitraz accounted for only a minimal percentage of the radioactivity (3-6%) in the gastric juice. A comparison of the metabolism of ^{14}C-amitraz in the rat, mouse, baboon, and human revealed that the urinary metabolic profile was similar among species. The results of the metabolism studies demonstrated that the metabolic pathway of amitraz in mammals involves hydrolysis to BTS 27271 and BTS 27919 with subsequent formation of the principal and terminal metabolite, BTS 28369. The chemical names of amitraz metabolites are listed in Appendix I, Table 2.

The acute oral toxicity of amitraz varied widely among the species tested (rats, mice, guinea pigs, rabbits, dogs, baboons, and pigs), with LD_{50} values reflecting high toxicity in dogs and pigs to low toxicity in mice. Non-rodents tended to be more sensitive than rodent species to the toxic effects of amitraz following administration of a single oral dose. In rats, amitraz was slightly acutely toxic via the dermal route and was of low acute toxicity via the inhalation route. It was minimally irritating to the eyes and skin of rabbits, and was determined to be a potential dermal sensitizer in guinea pigs using the maximization protocol.

Preventic Tick Collar for Dogs was of low acute toxicity via the oral route in rats and via the dermal route in rabbits. It was non-irritating to the skin of rabbits, and it was not a dermal sensitizer in guinea pigs using the Buehler protocol. Based on the physical form of the product, which is a plastic collar impregnated with amitraz, it is not considered to pose an acute inhalation or an eye irritation hazard.

A safety-to-treated-animals study in beagle puppies was available. Puppies wore collars that were considered to be representative of Preventic Tick Collar for Dogs in terms of the formulation constituents. The puppies wore one, three, or five collars, representing one (1×), three (3×), and five (5×) times the proposed application rate, respectively, for 30 days. Decreased food consumption was noted in male puppies from the 5× group. Puppies of both sexes in this group also demonstrated slight increases in blood glucose and urea nitrogen levels. In puppies from the 3× group, marginal increases in blood glucose and urea nitrogen occurred in only one sex and/or at very few time points. In determining the level of concern for these findings, it was noted that no clinical signs of toxicity or effects on body weight were observed in any of the treatment groups. On the basis of an assessment of the overall information, the level of concern with regards to safety to dogs wearing Preventic Tick Collar for Dogs was low.

While acceptable repeated-exposure studies conducted via the dermal and inhalation routes were not available for amitraz, the overall information provided in the toxicology database was considered sufficient to establish endpoints for risk assessment purposes.

In short-term oral toxicity studies conducted with amitraz via gavage and dietary administration, both mice and rats exhibited reduced body weight and body weight gains. Liver toxicity was observed in mice. Gavage dosing of rats with amitraz resulted in clinical signs of toxicity (irritability, excitability, aggressive behaviour, squealing), whereas dietary administration resulted in increases in absolute organ weights and changes in clinical chemistry parameters. Whether dosed for 90 days or two years, dogs administered amitraz via capsule demonstrated depression of the central nervous system (CNS), decreased heart rate, and reduced body temperature at similar doses.

The dog appeared to be the most sensitive laboratory species tested with respect to effects on the nervous system. As a point of note, in ERC2013-04 the 90-day and two-year dog studies are incorrectly reported as dietary studies. In addition, upon re-examination of the data, the 90-day study is now considered supplemental due to the small group sizes used.

Several mutagenicity studies conducted with amitraz failed to demonstrate a potential for mutagenic activity; studies included microbial point mutation assays, a dominant lethal study with male and female mice, a micronucleus study in mice, an unscheduled DNA synthesis assay in human embryonic cells, and a cell transformation assay. A mouse lymphoma mutation assay yielded equivocal positive findings at cytotoxic levels. Overall, amitraz was not considered to be genotoxic.

With chronic (two-year) dietary dosing of amitraz, mice demonstrated effects on the stomach (hyperkeratosis of the forestomach in males and prominence of the limiting ridge of the stomach in females) as well as reductions in body weight gain and food consumption. Male mice also exhibited aggressive behaviour and female mice were shown to have reduced ratios of myeloid to erythroid in the bone marrow. In rats, effects in a two-year dietary study were limited to abnormal behaviour (nervousness, excitability) and reduced body weight in both sexes, and convulsions in males.

There was no evidence of oncogenicity in rats exposed to amitraz via the diet for two years. In mice, dietary dosing with amitraz over two years resulted in increased incidences of hepatocellular adenomas and carcinomas in females, and lung adenomas in males, at the highest dose level tested. However, based on reductions in body weight gains noted after 18 months of dosing, it was concluded that the highest dose in the mouse study exceeded the maximum tolerated dose . Therefore, the tumour response observed in mice at the highest dose tested was not considered to be toxicologically significant. Overall, the weight of evidence supported the conclusion that amitraz was not carcinogenic.

In the acute oral neurotoxicity study in rats, decreases in body weight early in the study as well as effects on motor activity on the day of dosing were observed down to the lowest dose tested. At higher doses, decreases in grip strength, hypersensitivity, hypoactivity, convulsions, and an inability to walk were noted, with some of these effects observed at one or two weeks following the single gavage administration. Findings similar to those observed in the acute neurotoxicity study were also noted in the recently-submitted rat 90-day dietary neurotoxicity study, but at lower dose levels. There was no evidence of pathological lesions of nervous system tissues in either of these studies.

In a published study examining the effects of amitraz on the levels of neurotransmitters in various brain regions, adult rats were given five daily gavage doses of amitraz. In all examined brain regions (hypothalamus, midbrain, hippocampus, striatum, prefrontal cortex), the turnover rates for norepinephrine, serotonin, and dopamine were decreased, resulting in elevated levels of these neurotransmitters and reduced levels of their metabolites. The results of this study demonstrated that amitraz can cross the blood-brain barrier.

Based on the observed effects of amitraz on motor function in a published study in which rats were also dosed with drugs known to alter CNS function, it was suggested by the study authors that the motor function effects are a consequence of the inhibitory effects of amitraz on monoamine oxidase activity. This study also demonstrated elevations in noradrenaline and dopamine, and decreased levels of homovanillic acid, a metabolite of dopamine.

Developmental toxicity studies conducted in rats and rabbits via gavage administration, as well as a supplemental dietary three-generation reproductive toxicity study in rats and a drinking water reproductive and developmental toxicity screening study in rats from the published literature, were available for amitraz. In the rat dose range-finding developmental toxicity study, decreased fetal weight was observed, and in a supplemental developmental toxicity study in rats, decreased mean litter size was noted. Developmental effects in both of these studies occurred in the presence of decreased maternal body weight gain. In a guideline developmental toxicity study in rats, increased embryonal deaths, reduced litter weight, and dilated ureters were observed in fetuses in the presence of food consumption and body weight gain reductions as well as ocular opacity in maternal animals. In ERC2013-04, reference is made to a treatment-related increased incidence of renal pelvic cavitation in rat fetuses from the guideline developmental toxicity study. As a result of a further examination of these effects, it is now determined that the increase in this finding was not toxicologically significant, based on lack of a dose response.

Developmental effects observed in supplemental gavage studies in rabbits included decreases in litter size and fetal body weight occurring in the presence of maternal effects (clinical signs or hepatocellular hypertrophy). In a guideline gavage developmental toxicity study in rabbits, abortions and total litter losses were noted at a dose that produced clinical signs of toxicity and body weight loss in maternal animals. The request to waive the requirement for a new developmental toxicity study in non-rodents (for example, rabbits) was granted based the weight of evidence available to assess the developmental toxicity of amitraz.

In a reproductive and developmental toxicity screening assay from the published literature, in which amitraz was administered to rats via drinking water, parental toxicity was evident in the form of clinical signs and decreased body weight. At the same dose level, effects on testicular and sperm parameters were observed in parental animals, including reduced weights of the testes, seminal vesicles, epididymides, and prostate, as well as reduced sperm motility and a slight decrease in sperm counts. Degenerative changes were noted in the testes of one rat. A decrease in the number of live pups born and an increase in postimplantation loss were observed at a dose level that resulted in parental toxicity.

In a supplemental three-generation dietary reproductive toxicity study in rats, effects in parental animals were limited to decreased body weight and food consumption in the P generation. At these same dose levels, P generation dams exhibited a decrease in the number of F1 offspring born per litter; a decreased viability index was also observed in F1 offspring. At the next lower dose level, lactation indices were decreased in offspring of all generations. A decrease in lactation index was also observed in the F3 generation at the lowest dose tested.

In a dose range-finding study for the rat EOGRTS, increased pup deaths were observed at doses resulting in clinical signs of toxicity (such as hyper-reactivity, hypoactivity, and hunched posture) in parental animals. Offspring also displayed whole body tremors beginning on postnatal day (PND) 8 (the day on which direct dosing of the pups was initiated) down to the lowest dose tested, a dose which did not result in parental toxicity.

In the definitive rat EOGRTS, toxicity to parental animals following gavage dosing was evident at the highest dose tested. This included reductions in body weight and food consumption, signs of general toxicity and/or neurotoxicity (decreased motor activity, rearing, and body temperature, increased reactivity, urine/fecal staining), and changes in coagulation and clinical chemistry parameters. In the early postnatal period, there was a slight increase in high dose pup deaths between PND 1 and 4; many of these were attributed to loss of the entire litter after observation of convulsions in the maternal animals on PND 1.

In the EOGRTS, offspring were gavage-dosed beginning on PND 7. At the highest dose tested, pup body weight gain was reduced up to/including PND 21, at which time a slightly reduced pup body weight was also observed. In male offspring sacrificed on PND 21, changes in brain morphometric measurements consisting of decreased thickness of the hippocampal gyrus and corpus callosum were observed at the high dose. Brain morphometric measurements were not evaluated in offspring from lower dose groups. The reduction in body weight in F1 offspring in the EOGRTS persisted at the high dose following weaning. Additional effects in these young adult animals included similar findings to those recorded in parental animals (decreased motor activity, rearing, and body temperature as well as increased reactivity and changes in coagulation and clinical chemistry parameters). Reduced size of the hypothalamic area was also recorded in F1 animals sacrificed on PND 90, as was neuronal degeneration in the amygdala of one female. All of the aforementioned effects in offspring occurred at a dose level that was also toxic to parental animals. It was noted that the whole body tremors that were recorded in the EOGRTS dose range-finding study were not observed in the definitive EOGRTS, despite the similar dose levels used in both studies.

At the next lower dose level in the EOGRTS, which did not result in parental toxicity, increased thyroid/parathyroid gland weights were observed in female offspring sacrificed on PND 21. Reductions in thyroxine hormone (T4) levels were also observed at this dose level in female offspring sacrificed on PND 90. It was recognized that the thyroid-related effects were observed in females only, occurred at different time points, and were without corroborative histopathology. However, the lowest observed adverse effect level (LOAEL) in female offspring was established on the basis of these findings in order to protect for potential effects on the thyroid.

Reproductive toxicity at the high dose in the EOGRTS included a reduced number of liveborn pups in F1 litters, as well as changes in estrous cycle and increases in absolute uterine weight and number of ovarian follicles in F1 females. According to Guidance Document 117[2] issued by the Organisation for Economic Cooperation and Development, effects on such parameters are considered potential triggers for the production of a second generation within the conduct of the

[2] Guidance Document on the Current Implementation of Internal Triggers in Test Guideline 443 for an Extended One Generation Reproductive Toxicity Study, in the United States and Canada.

EOGRTS. The concern for the absence of a second generation in this study was low, given that the magnitude of the above-noted high-dose effects was slight and that the evidence within the amitraz database that subsequent generations were more sensitive than the first was not compelling. Furthermore, the points of departure selected for human health risk assessment are considered protective of potential effects on subsequent generations.

In a published study examining the effects of prenatal and postnatal amitraz exposure on levels of neurotransmitters (norepinephrine, dopamine, and serotonin) in various brain regions of offspring, pregnant rats were given daily gavage doses of amitraz during gestation and lactation. In offspring sacrificed on PND 60, changes in the content and metabolism of all three neurotransmitters were recorded in various brain regions. The response was not fully consistent among brain regions or between sexes, but the results suggested that maternal exposure to amitraz can alter noradrenergic, serotonergic, and dopaminergic neurochemistry in offspring, which in turn may lead to functional alterations. Changes in neurochemistry were noted in the prefrontal cortex, striatum and hippocampus, regions of the brain that are linked to processes of learning and memory. The toxicological database does not include an assessment of the potential effect of amitraz exposure on the development of learning and memory.

The developmental and behavioural effects from prenatal amitraz exposure were examined in a published study in rats, in which dams were gavage-dosed with amitraz every three days during the gestation period. In offspring born to control dams that were cross-fostered to treated dams, decreased time to fur development was observed. The offspring born to treated dams that were cross-fostered to control dams demonstrated decreased time to vaginal opening. Offspring born to treated dams that were cross-fostered to treated dams exhibited decreased time to fur development, delayed incisor eruption and decreased time to vaginal opening, increased locomotion and rearing, and decreased immobility time. These results suggested that prenatal exposure may accelerate the onset of some developmental milestones and delay others.

In a published study, neonatal rats of dams exposed to amitraz via gavage during the lactation period displayed delayed onset of some developmental milestones (fur development, eye opening, testis descent, startle response, and motor activity behaviour such as raising the head, shoulder and pelvis). Changes in some neurobehavioural parameters (increased time required to perform surface righting reflex, increased motor activity counts) were also observed in offspring of treated dams.

Overall, the toxicology database for amitraz is considered to include the relevant studies required to establish endpoints for risk assessment purposes. With regards to developmental neurotoxicity, however, there remains residual concern. This is based on the fact that effects on motor activity and changes in brain morphometric measurements were observed in high-dose offspring in the EOGRTS, and there is evidence from the published literature that amitraz can alter neurotransmitter levels in the brains of developing rats. Furthermore, brain morphometry was not conducted for offspring from the intermediate dose groups and, although not specifically required in the EOGRTS protocol, there was no assessment of learning and memory or of motor activity (at weaning). In light of this residual uncertainty, a 3-fold database uncertainty factor was applied to the points of departure selected for human health risk assessment.

Special studies were conducted to investigate the effects of dietary exposure to amitraz on the thymus, thyroid gland, estrous cycle, and hormone levels of mice after 28 or 33 weeks of dosing. The 28-week study included an examination of estrous cycle length, thyroid hormones, and levels of dehyroepiandrosterone, as well as several female reproductive hormones (follitropin, lutropin, prolactin, estradiol, testosterone, progesterone). In that study, there were an increased number of amitraz-treated animals in proestrus and a decreased number of animals in diestrus. In addition, there were increased dehydroepiandrosterone levels and decreased prolactin levels associated with amitraz treatment, but no effect was observed on estrous cycle length. Also in the 28-week study, an increase in the uptake of thyroid hormone, indicating a higher number of unsaturated T4 binding globulins in the blood, was observed; however, there was no effect on the circulating levels of T4 or triiodothyronine (T3) associated with amitraz. The highest dose tested in the 28-week study was lower than that used in the 33-week study, which included the assessment of estrous cycle length, β-estradiol levels, and thymus weight and histology. In the 33-week study, longer estrous cycles, a higher number of animals in prolonged estrous, and enlarged spleen and lymph nodes were observed in amitraz-treated mice. Amitraz did not adversely affect the circulating levels of β-estradiol in female mice, or the weight or histology findings for the thymus. In rats administered amitraz-treated diet for 18 weeks, increased estrous cycle length was also observed.

In a published study, lipid peroxidation, hepatotoxicity, and adverse effects on lipid synthesis in the liver were observed in rats following single or repeated (40-day) gavage dosing with amitraz. Increased serum glucose levels were also observed after administration of a single dose. Induction of the cytochrome P450 enzyme system occurred after repeated dosing only. No induction of hepatic mixed-function oxidases was observed in a special study in which mice were gavage-dosed with amitraz for four days.

The immunotoxicological effects of amitraz in rats after 28 days of gavage administration were reported in the published literature. Maximum delayed-type hypersensitivity reaction, as measured by decreased footpad thickness, was observed 24 hours after antigen injection. The number of spleen cells and the number of plaque-forming cells per spleen were reduced in amitraz-treated rats immunized with sheep red blood cells; however, no effect on the number of plaques formed was observed when normalized for the number of spleen cells.

Limited toxicity studies were available for three rat and plant metabolites of amitraz, namely BTS 27271, BTS 27919, and BTS 28369, as well as for the degradate BTS 24868, also known as 2,4-dimethylaniline. The toxicology data indicate that BTS 27271, which has been identified as the toxicologically active moiety of the amitraz molecule, is more potent than amitraz. On a molecular basis, BTS 27271 represents half of the amitraz molecule; therefore, oral administration of amitraz would be equivalent to approximately half the amount when expressed as BTS 27271. In addition to amitraz, the toxicological endpoints accommodate BTS 27271 when expressed as amitraz equivalents. Overall, the results of the studies for these metabolites and degradate did not suggest the potential to produce adverse effects beyond those already demonstrated by the comprehensive toxicity assessments of the parent molecule amitraz.

With regards to the degradate BTS 24868, reports on the assessment of the carcinogenic potential in male rats and male and female mice are available. Some of these reports identify positive findings. However, the available information is limited and contradictory in that a

different tumour type was identified in each report. Overall, the level of concern for degradate BTS 24868 is low, given that it has been detected at very low levels in environmental matrices, is present as an impurity in the technical grade active ingredient used in toxicity testing, and is likely present as a degradate in the amitraz test diets that were used for toxicity testing.

The PMRA has concluded that although two studies using human subjects were available for amitraz, both clearly assessed systemic toxicity. Accordingly, consistent with current policy (Science Policy Note SPN2016-01), these human studies were not used by the PMRA in the evaluation of amitraz. Both of these studies were also considered to be of limited scientific quality. Notwithstanding the above, the data do suggest that humans may be slightly more sensitive to a single bolus dose of amitraz than animals. This interspecies sensitivity is accounted for by the use of the standard 10-fold uncertainty factor for interspecies extrapolation.

Results of the toxicology studies conducted on laboratory animals with Preventic Tick Collar for Dogs, amitraz, and metabolites of amitraz are summarized in Tables 3, 4 and 5, respectively, of Appendix I. The revised toxicology reference values for use in the human health risk assessment are summarized in Table 6 of Appendix I.

Incident Reports

As of 3 April 2017, one minor human incident and 12 domestic animal incidents involving amitraz were received by the PMRA. All incidents occurred following the use of pet collars containing amitraz. The human incident reported a transient skin reaction following application of a collar to a dog. Seven of the 12 domestic animal incidents had at least some association between the effects and the reported exposure. Three of these incidents occurred in Canada and were minor or moderate in nature. In these three incidents, lethargy and anorexia occurred when the collar was applied to or chewed by the dog. When a piece of the collar was ingested, ataxia was also reported. The other four incidents occurred in the US. Death was reported in one dog that was treated with a Preventic collar; this dog was also treated at the same time with a spot-on flea control product. Stillbirths and birth defects were reported after a pregnant dog had been treated with Preventic. Serious effects such as bradycardia, seizure, hypothermia, and labored breathing were reported in kittens that came in contact with treated dogs and in a dog treated with Preventic that had an underlying medical condition.

Over a nine-year period, the Agency has received only 12 domestic animal incidents, and those incidents that were considered to be related to amitraz exposure account for approximately one incident per year. Although serious and fatal outcomes were reported in four incidents that occurred in the United States, there was no pattern in these incidents that might be used to determine possible mitigations. The overall low number of incidents and variability in the effects did not warrant risk mitigation, including label changes, at this time. Overall, the incident reports did not impact the current assessment.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, guideline developmental toxicity studies in rats and rabbits, and an EOGRTS which included a developmental neurotoxicity component, were included in the amitraz database. In addition, several supplemental developmental and reproductive toxicity studies with amitraz were available, including a developmental toxicity study in rabbits, a three-generation reproductive toxicity study in rats, a developmental and reproductive screening study in rats, and published studies investigating developmental, neurobehavioural, and neurochemical parameters in young rodents.

With respect to potential prenatal and postnatal toxicity, effects on fetal and offspring viability were noted in several studies. In the guideline rat and rabbit gavage developmental toxicity studies, a serious effect (an increase in fetal loss) was observed in the presence of maternal toxicity (for example, reduced body weight gain). Other developmental findings included dilated ureters in fetuses in the guideline rat developmental toxicity study which occurred at doses resulting in increased fetal loss. Effects on fetal viability in the presence of maternal toxicity were also observed in the supplemental rat and rabbit gavage developmental toxicity studies, as well as the rat reproductive toxicity screening study in which parental animals were administered amitraz via drinking water. In the supplemental three-generation dietary reproductive toxicity study in rats, a serious effect in the young (reduced postnatal survival) was observed at non-toxic parental doses.

In the dose range-finding study for the EOGRTS, tremors were observed in pups at a dose not resulting in toxicity to parental animals. In the definitive EOGRTS, effects in the offspring (perturbations to the thyroid gland) were observed at a dose that did not produce parental toxicity. At the high dose, offspring effects including decreased motor activity as well as more serious effects such as changes in brain morphometry and increased pup deaths were observed in the presence of maternal toxicity (convulsion, decreased motor activity).

In published studies, it was determined that prenatal or postnatal exposure to amitraz accelerated the onset of some developmental milestones (for example, vaginal opening) and delayed others (for example, incisor eruption) in the young. In another study, changes in the content and metabolism of the neurotransmitters norepinephrine, serotonin, and dopamine were recorded in various brain regions of offspring of dams exposed to amitraz during gestation and early lactation. Many of the affected brain regions are involved in processes of learning and memory. No maternal effects were reported in these published studies.

In light of the above-noted findings, uncertainty remains regarding the potential for developmental neurotoxicity from exposure to amitraz. This is due to the fact that brain morphometric measurements were not obtained for offspring from the intermediate dose groups

in the EOGRTS, and there was no assessment of motor activity at weaning or of adverse effects on learning and memory. These uncertainties were addressed through the application of a database uncertainty factor of 3-fold in the risk assessment. The toxicological endpoints selected for risk assessment provide adequate margins to the identified endpoints of concern and thus the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose

An acute reference dose was not required.

3.3 Acceptable Daily Intake

An acceptable daily intake was not required.

Cancer Assessment

Overall, the evidence in the available genotoxicity studies suggested that amitraz does not have genotoxic potential. Chronic dosing with amitraz resulted in lung tumours in male mice and liver tumours in female mice at excessive doses that were deemed not relevant to human health risk assessment. Therefore, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.

3.4 Residential Risk Assessment

3.4.1 Toxicological Reference Values

Although the database did not contain an acceptable repeat-dose dermal toxicity study, for dermal risk assessments of all durations, the NOAEL of 0.25 mg/kg bw/day from the two-year oral (capsule) toxicity study in dogs was considered acceptable for assessing the risk. Effects at the LOAEL of 1.0 mg/kg bw/day in the two-year dog study included CNS depression, as well as decreased body temperature and slowed pulse rate. These effects were observed after a single dose, with onset of toxic signs within a few hours of dosing, and were generally found to rapidly reverse and recur after each daily dose. They were therefore considered relevant for all durations of exposure.

For the assessment of risk to children from non-dietary (incidental) oral ingestion, the NOAEL of 0.25 mg/kg bw/day from the two-year oral (capsule) toxicity study in dogs was selected. Effects at the study LOAEL of 1.0 mg/kg bw/day included CNS depression, as well as decreased body temperature and slowed pulse rate. The effects at the LOAEL were observed after a single dose with onset of clinical signs of toxicity occurring within a few hours of dosing, and were generally found to rapidly reverse and recur after each daily dose.

The target margin of exposure (MOE) for dermal and incidental oral exposure scenarios is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as an additional 3-fold database uncertainty factor to account for residual uncertainty pertaining to developmental neurotoxicity.

This endpoint and target MOE provide margins of greater than 3000 to the points of departure for fetal loss in developmental toxicity studies in rats and rabbits, greater than 1800 to the dose resulting in reduced postnatal survival in the supplemental three-generation reproductive toxicity study in rats, greater than 600 to the point of departure for thyroid perturbations in offspring in the EOGRTS, and greater than 1800 to the point of departure for decreased offspring viability and changes in brain morphometry in the EOGRTS.

Toxicological reference values were not required to assess risk from exposure to amitraz via the inhalation route for the dog collar use since inhalation exposure is expected to be negligible.

3.5 Occupational and Residential Risk Assessment

3.5.1 Toxicological Endpoints

Residential applicator exposure is characterized as short-tem, and postapplication exposures to Preventic Tick Collar for Dogs are characterized as short- to intermediate-term, and are predominantly by the dermal route, and also by the incidental oral route for children (1 < 2 years of age).

3.5.1.1 Dermal Absorption

The dermal absorption value was derived from a rat *in vivo* dermal absorption study using a wettable powder formulation suspended in water. The application rate of 0.1mg/rat (9.8µg/cm^2) and longest monitoring interval (120 hours) were used to determine the dermal absorption value. Considering the available data and lack of formulation-specific dermal absorption information (wettable powder suspension compared to an impregnated plastic), a dermal absorption value of 18% is considered appropriate for the dermal risk assessment.

3.5.2 Residential Exposure and Risk Assessment

3.5.2.1 Handler Exposure and Risk Assessment

Adults have potential for exposure to the Preventic Tick Collar for Dogs during application.

Residential applicator exposure occurs for adults (16<80 years of age), primarily by the dermal route, while handling and applying the collars to dogs. Exposures to homeowners applying Preventic Tick Collar for Dogs are expected to be short-term in duration. A pet owner is assumed to apply no more than two collars per day. Inhalation exposure was considered negligible.

Dermal exposure to amitraz while handling a collar is estimated using the United States Environmental Protection Agency (USEPA) Residential Standard Operating Procedures (SOP) (October 2012), *Treated Pets*, applicator unit exposure coupled with the maximum amount of amitraz in a collar (TABLE 3.5.3.1-1).

Table 3.5.2.1-1 Homeowner applicator exposure and risk assessment when handling the Preventic Tick Collar for Dogs containing amitraz

Total amount of amitraz in collar[a] (kg a.i./pet)	Number of Collars Applied	Dermal Unit Exposure (mg/kg a.i.)	Dermal Exposure (mg/day)	Dermal Absorbed Dose[b] (mg/kg/day)	Dermal MOE[c] (target = 300)
0.002475	2	264.55	1.309	0.0029	85

a. Total amount of active ingredient contained in a collar (from labels) = collar weight (27.5g) x guarantee (9%) of active ingredient

b. Dermal Absorbed Dose = Dermal unit exposure (µg a.i./pr. gloves) or (Total amount of active in collar x dermal unit exposure (mg/kg a.i.)) x 2 collars per day x dermal absorption / adult body weight

Default number of two pets treated in a day (USEPA Residential SOP, 2012, *Treated Pets*); one collar per pet

adult body weight of 80kg; dermal absorption value: 18%

c. MOE = NOAEL / Dermally Absorbed Dose; $NOAEL_{oral}$ = 0.25 mg/kg bw/day

Although the target MOE (300) was not met, the risk assessment is considered very conservative. While the risk assessment was conducted using a liquid spot-on product as a surrogate, the amitraz is impregnated in the solid collar matrix. Submitted data also indicate slow release of the active from the collar. Therefore, only a fraction of the amount of amitraz in the collar is expected to be available for dermal transfer to the applicator. Considering the conservative nature of the applicator exposure estimation, the risks to applicators handling the collars are not of concern.

3.5.2.2 Post-application Exposure and Risk Assessment

There is potential for exposure to adults, youth, and children when petting, playing with, and grooming dogs wearing the Preventic Tick Collar for Dogs. The primary route of postapplication exposure when contacting treated pets is through the dermal route. Hand-to-mouth, non-dietary exposure for children (1<2 years of age) may also occur. The duration of exposure is considered to be short- to intermediate-term.

3.5.2.2.1 Residential Dermal Exposure and Risk Estimates

The residential postapplication dermal exposures were based on a dog stroking study. Estimated hand residue loading was adjusted according to age group. Dermal loading on hands is combined with the exposure duration from the Exposure Factors Handbook (2011) and normalized by age-specific body weight.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 300.

Stroking Study after Application of a Collar

The study was designed to collect data on the residue transferred to a gloved hand when petting a dog wearing a collar containing amitraz. The collars used as part of this study contained the same concentration (µg/g) of amitraz as the registered dog collar.

A single-size adjustable collar for dogs (62cm length; 27.5 g; 9% nominal guarantee of amitraz) was applied to two adult beagles on study day 0. The dogs were stroked on day 15 or 16. Stroking was performed by stroking the hair 10 times (from head to base of tail) by a person with one hand wearing a cotton glove. Stroking was assumed to include contact with the impregnated collar. The amitraz was extracted from the gloves using acetonitrile before analysis by high performance liquid chromatography.

Although this is a non-guideline study, the sample size (n=2) is not comparable to the United States Environmental Protection Agency Occupational and Residential Exposure Test Guidelines: OPPTS 875.2000 Group B – Postapplication Exposure Monitoring Guidelines: Study Design, which requires 5 replicates per day postapplication (up to 3 days postapplication). However, the application rate was relevant to the registered use pattern, and the stroking event did take place within the period that the dog would be wearing a collar.

The major limitations noted from this study were: a) Too few replicates; and b) not enough time intervals monitored to determine time of peak residues. Minor limitations included: a) Stroking conducted in only one direction which may under-estimate dermal exposure and, as such, did not reflect typical human-pet interactions; b) lack of range in dog sizes and neck sizes to determine differences in exposures; and c) lack of raw data, in order to confirm results. The mean residue transferred to gloves on the day of the stroking event was 0.150mg amitraz (SD±0.004).

However, it is likely that residue on the hair will increase beyond day 16 and therefore the exposures to people coming in contact with dogs wearing the collar may be under-estimated over the 90-day expected duration when the pet is wearing a Preventic Tick Collar for Dogs. Despite these limitations, this study was deemed the best available for use in a postapplication risk assessment (Table 3.5.3.2.1-1).

Table 3.5.2.2.1-1 Exposure and risk estimates for postapplication dermal contact with dogs wearing amitraz-impregnated collars

Animal Size	Lifestage (years of age)	Residue (mg a.i./glove/ stroking event) [b]	Adjusted Residue (60 strokes equivalence) (mg/h) [c]	Relative Human Hand SA ratio [d]	Exposure Time [e] (h/day)	Exposure (mg/day)	Dermal Absorbed Dose [f] (mg/kg/day)	Dermal MOE [g] (target = 300)
Study (~12.5kg) [a]	Adult	0.150	0.900	1	0.77	0.693	0.0016	160
	Youth (11 <16)	0.150	0.900	0.81	0.92	0.670	0.0021	120
	Child (1 <2)	0.150	0.900	0.34	1	0.303	0.0050	50

a. Only one length of product to fit a variety of dog sizes: Assumption that the length of collar worn is proportional to dog size, and the stroking regime is the same (i.e., equivalent area is being stroked on all dogs), then post-app exposure to sub-populations will likely be the same, for all dogs;
b. Assumption that the length of collar worn is proportional to dog size (i.e. dog surface area) and area stroked is also proportional to the residue rubbed off during stroking; therefore, risk assessment indicative of all dog sizes.
c. Residue x 6 to adjust the Residue from the10-stroke event to the equivalent of 60 strokes in an hour;
d. Adjustment (unitless) from typical adult hand ($0.089m^2$) conducting stroking event to youth ($0.072m^2$) and child ($0.03m^2$);
e. Exposure time from the Exposure Factors Handbook (2011);

f. Dermally Absorbed Dose (mg/kg bw/day) = Adjusted Residue * Hand Surface Area Ratio * Exposure Time * Dermal Absorption / Body Weight
Where,
Dermal Absorption: 18%
Body Weight = adult, 80kg; youth, 57kg; child, 11kg

g. Margin of Exposure (MOE) = NOAEL / Dermally Absorbed Dose; $NOAEL_{oral}$ = 0.25 mg/kg bw/day.

Risks are a concern for adults, youth, and children who are expected to pet, groom, and play with dogs wearing a Preventic Tick Collar for Dogs.

3.5.2.2.2 Toddler Hand-to-Mouth Exposure Estimates

Toddler hand-to-mouth exposure is estimated from hand contact with treated dogs and then putting fingers into the mouth. Exposure estimates are based on the USEPA Residential SOP (2012) hand-to-mouth equations (Table 3.5.2.2.2-1).

Table 3.5.2.2.2-1 Risk estimates for child (1<2 years of age) hand-to-mouth exposure following contact with a dog wearing an amitraz-impregnated collar

Dog Size	Dermal Exposure[b] (mg/hour)	Hand residue loading[c] (mg/cm^2)	Oral Dose[d] (mg/kg/day)	Hand-to-Mouth Risk[e] (target MOE = 300)
Study (~12.5kg)[a]	0.303	0.303	0.00345	72

a. Only one length of product to fit a variety of dog body sizes: Assumed that the length of collar worn is proportional to dog size, and the stroking regime is the same (i.e., equivalent area is being stroked on all dogs), then post-app exposure will be the same, for all dogs
b. Dermal Exposure (mg/hour) = Exposure (mg/day) / Exposure Time (1 hour/day) from postapplication dermal exposures
c. Hand residue loading (mg/hour) = Dermal Exposure (mg/hour); all of the residue from contact with treated dog is assumed to be on the hand
d. USEPA Residential SOP, Treated Pets; Post-application Non-Dietary Ingestion Exposure Assessment: Hand-to-Mouth Algorithms
e. Margin of Exposure (MOE); incidental (all durations) $NOAEL_{oral}$ is 0.25mg/kg bw/day

A risk of concern exists for toddler hand-to-mouth exposure following contact with dogs wearing Preventic Tick Collar for Dogs.

3.5.2.3 Aggregate Exposure and Risk Assessment

Dermal risks to adults, youth, and children are a concern following exposure to dogs wearing the Preventic Tick Collar for Dogs. Therefore, a residential aggregate risk assessment was not conducted.

3.6 Human Health and Safety Summary

The toxicology database submitted for amitraz is adequate to define the majority of toxic effects that may result from exposure. In short- and long-term studies with adult animals, the targets of toxicity were the liver and central nervous system. The dog appeared to be the most sensitive laboratory species tested. Chronic dosing with amitraz resulted in lung tumours in male mice and

liver tumours in female mice at excessive doses that were deemed not relevant to human health risk assessment. Reduced fetal and offspring viability was observed in several studies, in all but one case in the presence of maternal toxicity. Slight perturbations of the thyroid occurred in the young animal. A concern for the potential effects of amitraz on the developing nervous system was identified on the basis of brain morphometric changes, effects on motor activity, and alterations in neurotransmitter levels in the brain observed in the young. The risk assessment takes these effects into account in determining the allowable level of human exposure to amitraz.

Residential exposures from handling pet collars, and residents, including children, coming in contact with treated dogs, are expected to result in risks of concern when the Preventic Tick Collar for Dogs is used according to label directions.

4.0 Impact on the Environment

The use of amitraz in dog collars does not pose a risk to the environment as environmental exposure is expected to be negligible.

5.0 Value

5.1 Value of Amitraz for Use in Pet Collars

Amitraz for use in pet collars is registered to control American and brown dog ticks on dogs. Many ticks are known as vector-borne diseases and products, such as pet collars, are one of the ways to help protect dogs from ticks.

5.2 Domestic Class Products

Only one end-use product containing amitraz for use in pet collars (Preventic Tick Collars for Dogs, Pest Control Product Number 24496) is registered under the authority of the *Pest Control Products Act* (Appendix I, Table 1).

5.2.1 Alternatives to Domestic Class Products

Amitraz is registered in Canada for control of American and brown dog ticks on dogs. Alternative active ingredients, which include active ingredients formulated in pet collars, shampoos and sprays, are available in Canada for control of ticks on dogs. In addition, veterinary drugs are also available for control of ticks on dogs.

6.0 Organisation for Economic Co-operation and Development (OECD) Status of Amitraz

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups member countries and provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member country to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

Amitraz is currently acceptable for use in other OECD member countries, including Australia, the United States, Japan, and New Zealand. The European Commission prohibited the use of amitraz as a plant protection product in 2004. However, the European Medicine Agency approved amitraz to be used as a veterinary drug on dogs.

7.0 Proposed Re-evaluation Decision

After a re-evaluation of the use of amitraz in pet collars, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing the cancellation of all amitraz uses in pet collars based on risks associated with human health.

8.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, and DACO tables can be found on the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra.infoserv@hc-sc.gc.ca.

List of Abbreviations

↑	Increased
↓	Decreased
µg	Microgram(s)
♀	Females
♂	Males
°C	degrees Celsius
5-HIAA	5-hydroxy-3-indolacetic acid (metabolite of 5-HT)
5-HT	serotonin
abs.	absolute
AD	administered dose
A/G	albumin/globulin
a.i.	active ingredient
ALK	alkaline phosphatase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
bw	body weight
bwg	Body weight gain
CAS	chemical abstracts service
CFLP	cleavase fragment length polymorphism
cm	centimetres
cm^2	centimetres squared
CNS	central nervous system
CYPB5	cytochrome b5 reductase
CYTC	NADPH-cytochrome c reductase/NADPH-cytochrome P450 reductase
DA	dopamine
DACO	data code
DNA	deoxyribonucleic acid
DOPAC	3,4-hydroxyphenylacetic acid (metabolite of DA)
EOGRTS	extended one-generation reproductive toxicity study
F_1	first generation
F_2	second generation
F3	third filial generation
fc	food consumption
fe	food conversion efficiency
FOB	functional observational battery
G6PD	glucose-6-phoshate dehydrogenase
g	gram(s)
GD	gestation day
GGT	gamma glutamyl transferase
HCT	hematocrit
HDL	high density lipoprotein
HGB	hemoglobin

HVA	homovanillic acid (metabolite of DA)
K	potassium
kg	kilogram(s)
K_{ow}	octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD	Lactation day
LD_{50}	lethal dose to 50%
LDL	low density lipoprotein
LOAEL	lowest observed adverse effect level
m^2	metres squared
MCV	mean corpuscular volume
mg	milligram(s)
MHPG	3-methoxy-4-hydroxyphenylglycol (metabolite of NE)
MoA	mode of action
MOE	margin of exposure
mPa	megaPascal
NE	norepinephrine
nm	nanometers
NOAEL	no observed adverse effect level
NZW	New Zealand White
OECD	Organisation for Economic Co-operation and Development
P	parental generation
PFC	plaque-forming cells
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	Post-natal day
PT	prothrombin time
rel.	relative
SD	Sprague-Dawley
SOP	standard operating procedure
T3	triiodothyronine
T4	thyroxine hormone
USEPA	United States Environmental Protection Agency
wc	water consumption
wt(s)	weight(s)

Appendix I

Table 1 Amitraz Products Registered in Canada as of 03 May 2017 for Use in Pet Collars

Regn No.	Marketing Class	Registrant	Product Name	Formulation	Guarantee (amitraz)
23485	Technical	Arysta Lifescience America Inc.	Amitraz Technical	Dust	97%
24496	Domestic	Virbac AH Inc.	Preventic Tick Collars for Dogs	Slow release generator	9%

Table 2 Metabolite Identification

Metabolite Identifier	Chemical name
BTS 24868	2,4-dimethylaniline
BTS 27271	N-(2,4-dimethylphenyl)-N′-methyl-formamidine
BTS 27919	2,4-dimethylformanilide
BTS 28369	4-amino-3-methylbenzoic acid
BTS 39098	4-formamido-3-methyl benzoic acid
BTS 31158	4-acetamido-3-methyl benzoic acid

Table 3 Toxicity Profile of Preventic Tick Collar for Dogs Containing Amitraz

Study Type / Animal / PMRA #	Study Results
Acute oral Rat (SD) PMRA 1858755	Low Toxicity LD_{50} > 5000 mg/kg bw
Acute dermal Rabbit (NZW) PMRA 1858754	Low Toxicity LD_{50} > 2000 mg/kg bw
Acute inhalation	Not considered to pose an acute inhalation hazard based on the physical form of the product (plastic collar impregnated with amitraz).
Eye irritation	Not considered to pose an eye irritation hazard based on the physical form of the product (plastic collar impregnated with amitraz).

Study Type / Animal / PMRA #	Study Results
Dermal irritation Rabbit (NZW) PMRA 1858753	Non-irritating
Dermal sensitization Guinea pig (Hartley) PMRA 1858751	Negative
Safety to treated animals Dog (Beagle) PMRA 1858748	Groups of 11- to 12-week-old puppies (6/sex/group) wore one (1× group), three (3× group), or five (5× group) collars containing 9% amitraz and 0.5% pyriproxyfen for 30 days. A placebo control group (6/sex) wore five placebo control collars (formulants only, active ingredients omitted) for 30 days. 3× Increases in blood glucose were seen in ♂ puppies on a few occasions. BUN levels were increased at the end of the study period when values for both sexes were combined. 5× Decreased fc was observed in ♂puppies during weeks 3 to 5 of the study. Blood glucose levels were elevated in ♂ and ♀ puppies throughout most of the study. BUN levels were also elevated in ♂ throughout the study and in ♀ on a few occasions.

Table 4 Toxicity Profile of Technical Amitraz

[Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.]

Study Type / Animal / PMRA #	Study Results
Acute Toxicity Various species PMRA 2720107, 1936905, 1231956, 1936911	The acute oral toxicity of amitraz varies widely among species, with oral LD_{50} values of 400-938 mg/kg bw in rats, >1600 mg/kg bw in mice, 400 to 800 mg/kg bw in guinea pigs, >100 mg/kg bw in rabbits, 100 mg/kg bw in dogs, 100 to 250 mg/kg bw in baboons, and 100 mg/kg bw in pigs. Amitraz is slightly toxic via the dermal route (LD_{50} > 1600 mg/kg bw in the rat), of low toxicity via the inhalation route (LC_{50} = 2.4 mg/L in the rat), minimally irritating to the eyes and skin of rabbits, and was determined to be a potential skin sensitizer in guinea pigs using the maximization protocol.

Study Type / Animal / PMRA #	Study Results
90-day oral (diet) Mouse (ICR-SLC) PMRA 1244634	Supplemental. 3 mg/kg bw/day: ↓ bw week 1 (♀). ≥12 mg/kg bw/day: ↓ bw, ↓ fc, ↑ incidence of presence of urobilinogen; ↓ wc, ↑ rel. heart wt (♂); ↑ A/G ratio, ↓ ALT, ↓ ALK, slight black change in liver (♀). 50 mg/kg bw/day: ↑ A/G ratio; ↑ rel. brain wt, slight black change in liver (♂); ↓ wc, ↓ rel. kidney wt (♀).
90-day oral (gavage) Mouse (CFLP) PMRA 1244635	NOAEL not established as effects were noted down to the lowest dose tested. ≥3 mg/kg bw/day: ↓ bwg during first and third weeks (♂); bw loss first and/or third week (♀). ≥12 mg/kg bw/day: ↓ reducing substances in blood, slight to moderate hepatocyte and/or nuclear enlargement; ↑ rel. kidney wt (♂). ≥50 mg/kg bw/day: bw loss during first two weeks, ↑ ALT, ↑ rel. liver wt; ↑ rel. spleen wt (♂); ↑ rel. kidney wt (♀). 200 mg/kg bw/day: ↑ mortality last 3 weeks of dosing, progressive emaciation and inactivity in dying animals, poor condition in survivors, ↓ HCT, ↓ HGB, bile duct proliferation, inflammatory infiltration into portal tracts of liver, presence of intranuclear inclusion; ↑ rel. spleen wt., granular appearance to surface of liver (♀).
90-day oral (gavage) Rat (Ash-Wistar) PMRA 1244615	NOAEL = 3 mg/kg bw/day 12 mg/kg bw/day: occasional irritability and excitability; slight ↓ bw (♂). 50 mg/kg bw/day: ↓ bw, excitability, aggression, squealing. <u>21-Day Recovery</u> 50 mg/kg bw/day: bw loss, ↓ bw (♂); ↑ bwg (♀).
90-day oral (diet) Rat (Wistar) PMRA 1244626	Supplemental. ≥12 mg/kg bw/day: ↓ fc, ↑ incidence of proteinuria; ↓ platelets, ↓ urinary K (♂); ↓ bw, ↓ wc (♀). 50 mg/kg bw/day: ↑ abs. wt of several organs; ↓ bw, ↓ wc, ↓ ALK, ↑ serum K (♂); ↓ eosinophils, ↓ AST, ↓ urinary K (♀).

Study Type / Animal / PMRA #	Study Results
90-day oral (capsule) Dog (Beagle) PMRA 1936920	Supplemental. ≥1 mg/kg bw/day: signs of CNS depression, ataxia, ↓ body temperature, ↓ heart rate, ↑ blood glucose. 4 mg/kg bw/day: occasional vomiting during last two days of dosing, ↑ urinary glucose, ↑ rel. liver wt, hyperplasia of small periportal hepatocytes, ↑ binucleated cells.
Two-year oral (capsule) Dog (Beagle) PMRA 1244611, 1244612, 1244613, 1244631	NOAEL = 0.25 mg/kg bw/day 1 mg/kg bw/day: signs of slight CNS depression in all dogs three hours post-dosing on days 1 and 2, ↓ heart rate, ↓ body temperature, ↓ monocytes, ↑ blood glucose, area of fibrosis around large duct of the liver in one dog, very slight subscapular fibrosis of the liver in one dog.
Two-year chronic toxicity / oncogenicity (diet) Rat (Ash-Wistar) PMRA 1244605, 1244606	NOAEL = 2.5 mg/kg bw/day 10 mg/kg bw/day: abnormal behaviour (nervous, excitable, aggressive), ↓ bw; convulsions in three animals (♂). No evidence of oncogenicity.

Study Type / Animal / PMRA #	Study Results
Two-year oncogenicity (diet) Mouse (B6C3F1) PMRA 1166816, 1166817	NOAEL in ♂ not established as effects were noted down to the lowest dose tested. NOAEL in ♀ = 2.6 mg/kg bw/day ≥2.3/2.6 mg/kg bw/day: forestomach hyperkeratosis (♂). ≥9.6/11 mg/kg bw/day: ↓ bwg, ↓ fc; aggressive behaviour (fighting; mainly during first three months, resulting in cutaneous lesions) (♂); ↓ myeloid/erythrocyte ratios in bone marrow smears, prominence of limiting ridge of stomach (♀). 45/50 mg/kg bw/day: ↑ mortality, ↑ fc (weeks 12 or 19 to 26); hyperactivity in eight ♂ first two weeks, urogenitial masses and swelling resulting from enlargement of preputial gland (result of fighting), hunched posture, piloerection, ↓ myeloid/erythroid ratios in bone marrow smears, ↑ lung tumours (♂); liver masses, ↓ incidence of gross uterine changes, hyperplastic nodules of liver, ↑ liver tumours (♀). <u>Hepatocellular adenoma</u> ♂: 6/100, 3/73, 2/75, 6/75 (6%, 4%, 3%, 8%) ♀: 4/100^{++}, 1/75, 2/75, 5/75** (4%, 1%, 3%, 7%**) [HC 4-14%] <u>Hepatocellular carcinoma</u> ♂: 14/100, 8/73, 6/75, 8/75 (14%, 11%, 8%, 11%) ♀: 2/100, 0/75^{++}, 1/75, 15/75** (2%, 0%, 1%, 20%**) [HC 4-6%] <u>Hepatocellular adenoma/carcinoma</u> ♀: 6/100^{++}, 1/75, 4/75, 26/75** (6%, 1%, 5%, 35%) [HC 8-20%] <u>Lung adenoma</u> ♂: 7/100^{++}, 12/73, 8/75, 16/75** (7%, 16%, 11%, 21%**) [HC 5-18%] ♀: 7/100, 8/75, 4/75, 10/75 (7%, 11%, 5%, 13%) $^{++}$ statistically significant trend ($p<0.01$) ** statistically significantly different from the control group ($p<0.01$) Evidence of oncogenicity (lung adenomas in ♂; hepatocellular adenomas and carcinomas in ♀) at a dose that exceeded the maximum tolerated dose (based on ↓ bwg >10% at week 78).
Developmental toxicity (gavage) with postnatal assessment Rat (Boots-Wistar) PMRA 1244617	Supplemental. Maternal animals were dosed from GD 0 to LD 20. <u>Maternal Toxicity</u> 12 mg/kg bw/day: ↓ bwg GD 0-20. <u>Reproductive Toxicity</u> 12 mg/kg bw/day: ↓ mean litter size on PND 0. <u>Offspring Toxicity</u> 12 mg/kg bw/day: ↓ mean litter size at PND 4 due to smaller litter size on PND 0 since no effect on viability index.

Study Type / Animal / PMRA #	Study Results
Developmental toxicity (gavage) – dose range-finding study Rat (SD) PMRA 1190339	NOAELs not established as study was a dose range-finding study. Maternal animals were dosed from GD 6 to 15. <u>Maternal Toxicity</u> ≥15 mg/kg bw/day: ↓ bw GD 6-15. 30 mg/kg bw/day: ↓ fc, slight unilateral hydronephrosis in one ♀. <u>Developmental Toxicity</u> ≥15 mg/kg bw/day: ↓ fetal wt. 30 mg/kg bw/day: one fetus with hemorrhagic areas on head.
Developmental toxicity (gavage) Rat (SD) PMRA 1190341, 1228857	Maternal animals were dosed from GD 6 to 15. <u>Maternal Toxicity</u> NOAEL = 7.5 mg/kg bw/day ≥15 mg/kg bw/day: ↓ bwg, ↓ fc, unilateral ocular opacity. 30 mg/kg bw/day: stained fur. <u>Developmental Toxicity</u> NOAEL = 15 mg/kg bw/day 30 mg/kg bw/day: ↑ embryonal deaths, ↓ live fetuses/litter, ↓ litter wt, dilated ureters. Serious developmental effect (embryo-fetal loss) in the presence of maternal toxicity.
Developmental toxicity (gavage) Rabbit (NZW) PMRA 1936947	Supplemental. Maternal animals were dosed from GD 6 to 18. <u>Maternal Toxicity</u> ≥5 mg/kg bw/day: enlarged hepatocytes. 25 mg/kg bw/day: four abortions (GD 17, 19, 19, 20), ↓ bwg, bw loss. <u>Developmental Toxicity</u> 25 mg/kg bw/day: slight ↓ live fetuses/litter, ↓ fetal bw.

Study Type / Animal / PMRA #	Study Results
Developmental toxicity (gavage) – dose range-finding study Rabbit (NZW) PMRA 1190340	NOAELs not established as study was a dose range-finding study. Maternal animals were dosed from GD 7 to 19. <u>Maternal Toxicity</u> ≥7.5 mg/kg bw/day: languor, lethargy, subdued state, shallow respiration, ataxia, ↓ bwg, ↓ fc. 15 mg/kg bw/day: one death GD 9. 30 mg/kg bw/day: three deaths (one found dead GD 9, two sacrificed following abortion GD 20 or 25), two abortions, one total litter loss, shallow respiration, ataxia, bw loss GD 7 to 13 in survivors. <u>Developmental Toxicity</u> 15 mg/kg bw/day: ↓ litter wt. 30 mg/kg bw/day: two abortions, one total litter loss, ↓ fetal bw, ↓ litter wt, major external defects in 4/8 fetuses in one surviving litter (three with a rudimentary tail, one with acaudia).
Developmental toxicity (gavage) Rabbit (NZW) PMRA 1190342, 1228856	Maternal animals were dosed from GD 7 to 19. <u>Maternal Toxicity</u> NOAEL not determined as effects were noted down to the lowest dose tested. ≥3 mg/kg bw/day: languor, polypnea, squinting of eyes. 12 mg/kg bw/day: two abortions (sacrificed GD 17 and 19), three total litter losses, bw loss, ↓ bwg, ↓ fc. <u>Developmental Toxicity</u> NOAEL = 6 mg/kg bw/day 12 mg/kg bw/day: two abortions, three total litter losses, ↑ intrauterine deaths. Serious developmental effect (embryo-fetal loss) in the presence of maternal toxicity.
Developmental toxicity (non-rodent) Waiver request PMRA 2668513	Request to waive the requirement for a new developmental toxicity study in non-rodents was granted based on the totality of information available to assess the developmental toxicity of amitraz.

Study Type / Animal / PMRA #	Study Results
Reproductive and developmental toxicity screening test (drinking water) Rat (SD) PMRA 2720265	Supplemental. Parental ♂ were dosed for two weeks pre-mating and during two-week mating period. Parental ♀ were dosed for two weeks pre-mating, during a two-week mating period, until LD 4. <u>Parental Toxicity</u> ≥12 mg/kg bw/day: ↓ fc. 36 mg/kg bw/day: clinical signs after 7 days of dosing (reddish tears, nasal discharge, fur staining, dull fur, nervousness), ↓ bw; ↓ seminal vesicle wt, ↓ abs. testis wt, ↓ abs. epididymal wt, ↓ abs. ventral prostate wt ↓ sperm motility, slight ↓ sperm count, degeneration of spermatocytes in testis in one rat, exfoliation of degenerative germ cells in epididymal ducts in 1 rat (♂). <u>Reproductive Toxicity</u> 36 mg/kg bw/day: ↓ live pups at birth, ↑ postimplantation loss. <u>Offspring Toxicity</u> 36 mg/kg bw/day: ↓ mean litter size at PND 4 likely due to smaller litter size on PND 0 as there was no mention of increased pup deaths PND 0 to 4, and litter size on PND 4 was comparable to that on PND 0.
Three-generation reproduction (diet) Rat (Boots-Wistar) PMRA 1149925, 1244619	Supplemental. Parental animals were dosed for ten weeks pre-mating. <u>Parental Toxicity</u> 20 mg/kg bw/day: ↓ bw P generation, ↓ fc first 2 weeks of dosing P generation. <u>Reproductive Toxicity</u> 20 mg/kg bw/day: ↓ F1 births/dam. <u>Offspring Toxicity</u> ≥1.5 mg/kg bw/day: ↓ F3 lactation index. 5 mg/kg bw/day: ↓ lactation index (F1, F2), ↓ bw F2 and F3 (only measured on PND 21). 20 mg/kg bw/day: ↓ F1 viability index, marked ↓ F1 lactation index.

Study Type / Animal / PMRA #	Study Results
Extended one-generation reproductive toxicity (gavage) - dose range-finding study Rat (SD) PMRA 2404307	NOAELs not established as study was a dose range-finding study. Parental ♂ were dosed for two weeks pre-mating, during two-week mating period, up to day 49. Parental ♀ were dosed for two weeks pre-mating, during two-week mating period, up to LD 7. Offspring were dosed from PND 8 to 23. <u>Parental Toxicity</u> ≥3 mg/kg bw/day: vocalization; ↓ bw, ↓ bwg, ptosis, urine-stained fur (♂); hypoactivity during gestation, ↓ bwg premating, ↓ fc during gestation, ↑ reaction to handling five hours post-dose day 1 (♀). ≥8 mg/kg bw/day: ↓ fc, clinical signs (hyper-reactivity to touch, hypoactivity, hunched posture), ↑ reaction to handling three to six hours post-dose day 6 (♂); ↓ fc premating, clinical signs (ptosis, urine-stained abdominal fur, hypoactivity, hyper-reactivity to touch, hunched posture), ↑ reaction to handling six hours post-dose day 1 and two to six hours post-dose day 6, ↓ rearing upon return to home cage three to six hours post-dose day 6, ↓ body temperature three to six hours post-dose (♀). 15 mg/kg bw/day: 1 ♂ died day 26, ↓ body temperature three to six hours post-dose (♂); ↓ bw premating and gestation, ↓ bw LD 1-7 (♀). <u>Reproductive Toxicity</u> 15 mg/kg bw/day: ↓ implantations/dam, ↓ pups/litter. <u>Offspring Toxicity</u> ≥1 mg/kg bw/day: whole body tremors PND 8 onward (♀). ≥3 mg/kg bw/day: whole body tremors PND 8 onward (♂); ↓ bw and bwg PND 8 to 23 (♀). ≥8 mg/kg bw/day: ↑ pup deaths PND 1 to 5, ↓ viability index (slight at 8 mg/kg bw/day), delay in attainment of air righting reflex, FOB findings (reduced activity, whole body tremors, unusual posture/behavior) most pronounced PND 13; ↓ bw and bwg PND 8 to 23 (♂); swollen limbs (♀). 15 mg/kg bw/day: slight ↑ pup deaths PND 8 to 23, ↓ lactation index, hypoactivity; swollen limbs (♂); mild dehydration (♀).

Study Type / Animal / PMRA #	Study Results
Extended one-generation reproductive toxicity (gavage) Rat (SD) PMRA 2668512	Parental ♂ were dosed for four weeks pre-mating, during two-week mating period, up to day 87. Parental ♀ were dosed for two weeks pre-mating, during two-week mating period, up to LD 21. Offspring were dosed from PND 7 onward. <u>Parental Toxicity – P Generation</u> NOAEL = 1.5 mg/kg bw/day 7.5 mg/kg bw/day: urine-stained abdominal fur, ↓ motor activity, ↑ ALK; ↑ salivation, ↑ vocalization upon touch, ↑ reaction to handling, ↓ rearing, unkempt appearance, urine/fecal staining, ↓ body temperature, ↓ fc throughout dosing period, ↓ bw throughout dosing period, ↓ APTT, ↓ PT, ↑ bilirubin, ↑ cholesterol, ↓ glucose (♂); ↓ fc first week of dosing, bw loss first week of dosing, convulsion in one ♀ on LD 1 (♀). <u>F1 Generation – Post-Weaning</u> NOAEL in ♀ = 0.5 mg/kg bw/day NOAEL in ♂ = 1.5 mg/kg bw/day ≥1.5 mg/kg bw/day: ↓ T4 PND 90 (♀). 7.5 mg/kg bw/day: ↓ bw, ↑ reaction to handling, ↓ rearing, ↓ motor activity, ↓ APTT, ↑ ALK; ↓ bwg, ↓ fc, ↓ urinary pH, ↓ size of hypothalamic area [not assessed at lower doses] (♂); ptosis, ↓ body temperature, ↑ AST, ↑ ALT, ↑ GGT, ↑ bilirubin, hepatocellular vacuolation, neuronal degeneration in the amygdala in one ♀ (♀). <u>Offspring Toxicity – F1 Generation</u> NOAEL in ♀ = 0.5 mg/kg bw/day NOAEL in ♂ = 1.5 mg/kg bw/day ≥1.5 mg/kg bw/day: ↑ thyroid/parathyroid gland weight PND 21 (♀). 7.5 mg/kg bw/day: ↑ pup deaths PND 1 to 5 [includes loss of six pups in dam that had convulsion on LD 1], ↓ viability index, ↓ bw PND 21, ↓ bwg PND 7-21; ↓ thickness of hippocampal gyrus and corpus callosum PND 21 [brain morphometry not assessed at lower dose levels] (♂). <u>Reproductive Toxicity</u> NOAEL = 1.5 mg/kg bw/day 7.5 mg/kg bw/day: slight ↓ number of F1 pups born live; ↓ abs. uterine wt (F1), slight ↑ number of F1 ♀ in persistent diestrus, slight ↑ number of F1 ♀ in proestrus, ↑ primordial follicles (F1) (♀). Serious effect in the young (pup deaths) in the presence of maternal toxicity (convulsion in one dam, ↓ motor activity).

Study Type / Animal / PMRA #	Study Results
Developmental and behavioural effects of prenatal exposure in rats (gavage) – cross-fostering study Rat (Wistar) PMRA 2720279	Supplemental. Maternal animals were dosed on GD 1, 4, 7, 10, 13, 16, and 19 (only one dose level was used). No treatment-related maternal effects were observed at 20 mg/kg bw/day. In offspring born to control dams that were cross-fostered to treated dams, ↓ time to fur development was observed. In offspring born to treated dams that were cross-fostered to control dams, ↓ time to vaginal opening was observed. In offspring born to treated dams that were cross-fostered to treated dams, ↓ time to fur development, delayed incisor eruption, ↑ locomotion PND 30, ↑ rearing PND 30, ↓ immobility time PND 30 and ↓ time to vaginal opening were observed. Results from this study suggest that prenatal exposure may accelerate onset of some developmental milestones (vaginal opening, fur development) and delay others (incisor eruption).
Developmental and behavioural effects of postnatal exposure in rats (gavage) Rat (Wistar) PMRA 2720280	Supplemental. Maternal animals were dosed on LD 1, 4, 7, 10, 13, 16, and 19 (only one dose level was used). No treatment-related maternal effects were observed at 10 mg/kg bw/day. Offspring effects at 10 mg/kg bw/day: delayed fur development, eye opening, testis descent, onset of startle response, more time required to perform surface righting reflex on PND 3 and 5, ↑ motor activity in open field PND 16 to 18, qualitative differences in motor activity (raising the head, shoulder and pelvis one or two days later). Results from this study suggest that postnatal exposure may delay onset of some developmental milestones.

Study Type / Animal / PMRA #	Study Results
Effects of prenatal and postnatal exposure on norepinephrine, serotonin, and dopamine levels in brain regions (gavage) Rat (Wistar) PMRA 2720165	Supplemental. Maternal animals were dosed from GD 6 to LD 10 (only one dose level was used). No treatment-related maternal effects were observed at 20 mg/kg bw/day. Offspring effects at 20 mg/kg bw/day: ↓ 5-HT and 5-HIAA levels in prefrontal cortex, ↓ 5-HT and 5-HIAA levels in striatum, ↑ 5-HIAA levels in medulla oblongata and hippocampus, ↓ NE and MHPG levels in prefrontal cortex and striatum, ↓ NE turnover in hypothalamus, ↓ DA in prefrontal cortex and hippocampus, ↓ DOPAC and HVA in prefrontal cortex, ↑ DOPAC and HVA in hippocampus, ↓ DA in striatum, ↑ DOPAC and HVA in striatum, ↑ DOPAC in midbrain, ↑ DA turnover in striatum and hippocampus; ↓ NE turnover in prefrontal cortex (♂); ↓ 5-HT turnover in prefrontal cortex, ↓ NE turnover in striatum (♀).
Acute neurotoxicity (gavage) Rat (SD) PMRA 2198090	NOAEL not determined as effects were noted down to the lowest dose tested. ≥50 mg/kg bw: ↓ bw day 1 to 2, ↓ bwg days 0 to 1, ↓ motor activity habituation day 0. ≥200 mg/kg bw: hypoactivity; soiled perioculus, bradpynea, ↓ forelimb grip strength days 7 and 14 (♂). 800 mg/kg bw: hypersensitivity to handling, abnormal reaction to touch day 7, abnormal reaction to pain day 7, ↓ hindlimb grip strength day 7, ↓ motor activity counts day 7; prone position, convulsion, increased reactivity to handling day 7, abasia (inability to walk) day 0 (♂); soiled perioculus, bradypnea (♀).
Subchronic (90-day) neurotoxicity (diet) Rat (SD) PMRA 2198091	NOAEL = 2.8/2.9 mg/kg bw/day in ♂/♀ ≥11 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↓ fe week 1; ↓ motor activity counts week 2 (♂); ↓ hindlimb grip strength (♀). 40/43 mg/kg bw/day: hypersensitivity, self-biting, distress upon handling, abnormal touch response, abnormal pain response, ↓ forelimb grip strength, ↓ motor activity counts; aggression, pale skin and eyes (blood loss resulting from self-biting), moribund condition (limping, lateral position, bradypnea, hypothermia) in one ♂ leading to early sacrifice during week 12, ↓ hindlimb grip strength, ↓ motor activity habituation week 13 (♂); urinary incontinence (♀).

Study Type / Animal / PMRA #	Study Results
Effects of amitraz on motor function and neurobiochemistry (single gavage dose) Rats (Wistar) PMRA 2720233	Supplemental. ≥20 mg/kg bw: ↑ apomorphine-induced stereotypy, ↑ sodium pentobarbital sleeping time. 100 mg/kg bw: changes in open field (↓ locomotion, ↓ rearing, ↑ immobility time 60 to 180 minutes post-dosing, ↑ noradrenaline (whole brain), ↑ dopamine (striatum), ↓ homovanillic acid (striatum and whole brain). Treatment with amphetamine accentuated the changes in the open field seen with exposure to amitraz; administration of metoclopromide was antagonistic to the effects of amphetamine on locomotion and rearing frequencies of amitraz-treated rats. Treatment with yohimbine had no effect on the amitraz-related changes in open-field behaviour. Treatment with metoclopramide completely antagonized apomorphine-induced stereotyped behaviour in amitraz-treated rats. The results of this study suggest that the amitraz effects on motor function are a consequence of its inhibitory effects on monoamine oxidase activity.
Effects on noradrenaline, serotonin, and dopamine levels in brain regions of 30 and 60 day old rats (five-day gavage) Rat (Wistar) PMRA 2720176	Supplemental. ≥20 mg/kg bw/day: ↑ 5-HT levels, ↓ 5-HIAA levels, ↓ 5-HT turnover rate, ↑ NE levels, ↓ MHPG levels, ↓ NE turnover rate, ↑ DA levels, ↓ DOPAC levels, ↓ HVA levels, ↓ DA turnover rate [all findings were observed in all brain regions examined: hypothalamus, midbrain, hippocampus, striatum, prefrontal cortex].
Effect on hepatic mixed-function oxidase system (four-day gavage) Mouse (B6C3F1) PMRA 1167719	Supplemental. Only one dose level was used. 100 mg/kg bw/day: moribund condition and hunched posture after first dose (more severe after second dose), ↑ liver wt, ↑ cytochrome b5. No induction of mixed-function oxidases was observed.

Study Type / Animal / PMRA #	Study Results
Effects on the thymus gland and estrous cycle (33-week dietary) Mouse (CFLP) PMRA1167708	Supplemental. Only one dose level was used. 106/136 mg/kg bw/day: ↓ bw, ↑ fc; fighting (♂); transient exudation from vagina, rapid/uneven respiration, longer estrous, ↑ number of mice in prolonged estrous, enlarged lymph nodes, enlarged spleen (♀). No effect on β-estradiol or thymus weight. No treatment-related histological lesions in ovaries, uterus, or pituitary gland.
Effects on estrous cycle and hormones (28-week dietary) Mouse (B6C3F1) PMRA 2720238	Supplemental. ≥15 mg/kg bw/day: ↑ dehydroepiandrosterone, ↓ progesterone, ↑ rel. liver wt (♀). 60 mg/kg bw/day: ↓ bw, ↑ number of animals in proestrus, ↓ number of animals in diestrus, ↓ prolactin levels, ↑ thyroid hormone uptake, ↓ BUN, ↓ serum glucose (♀). No effect on estrous cycle length.
Effect on estrous cycle of rat (18-week dietary) Rat (strain unknown) PMRA 2720238	Supplemental. Only one dose level was used. 10 mg/kg bw/day: ↑ estrous cycle length
Immunotoxicological effects in rats (28-day gavage) Rat (Wistar) PMRA 2720237	Supplemental. ≥21mg/kg bw: ↓ MCV, ↓ footpad thickness at 24 hours. 27 mg/kg bw: ↑ rel. adrenal wt, ↓ spleen cell number, ↓ PFC/spleen. No effect on PFC/10^6 spleen cells.

Study Type / Animal / PMRA #	Study Results
Effects on serum biochemical, oxidative stress, and drug-metabolizing parameters (single and 40-day gavage) Rat (Wistar) PMRA 2720254	Supplemental. Only one dose level was used for each dosing regimen. Single dose at 170 mg/kg bw: ↑ malondialdehyde (in the liver, brain, spleen, testis, and erythrocytes), ↑ nitric oxide (in the liver, kidney, brain, spleen, and testis), ↓ superoxide dismutase (in the liver, kidney, brain, spleen, and erythrocytes), ↓ catalase (in the kidney and spleen), ↓ glutathione peroxidase (in the liver, kidney, brain, spleen, testis, and erythrocytes), ↑ glucose, ↓ HDL, ↑ LDL, ↑ AST, ↑ ALK, ↓ G6PD. 40-day dosing 25 mg/kg bw/day: ↑ malondialdehyde (in the liver, kidney, brain, spleen, testis, and erythrocytes), ↑ nitric oxide (in the liver, kidney, brain, spleen, and testis), ↓ superoxide dismutase (in the liver, kidney, brain, spleen, testis and erythrocytes), ↓ catalase (in the liver kidney, brain, spleen, testis and erythrocytes), ↓ glutathione peroxidase (in the liver, kidney, brain, spleen, testis, and erythrocytes), ↑ glucose, ↑ triglycerides, ↑ LDL, ↑ AST, ↑ ALT, ↑ ALK, ↓ total protein, ↓ albumin, ↑ CYP2E1, ↑ CYPB5, ↑ CYTC, ↓ G6PD, ↓ glutathione.
Genotoxicity PMRA 1166799, 1166800, 1166801, 1166806, 1166807, 1166808, 1166810, 1244614, 1936950, 1936951, 1936952, 1166804, 2720281	Overall negative for genotoxic potential. Several mutagenicity studies conducted with amitraz failed to demonstrate potential for mutagenic activity. These studies included microbial point mutation assays, a dominant lethal study with male and female mice, a micronucleus study in mice, an unscheduled DNA synthesis in human embryonic cells and a cell transformation assay. A mouse lymphoma mutation assay yielded equivocal results at cytotoxic levels.
Toxicokinetics Mouse (CFLP) PMRA 2720107	Preliminary studies conducted in CFLP mice demonstrated rapid metabolism and excretion. Within 48 hours of administration, 70-90% of a single oral dose was eliminated, with 44-53% of the AD in urine and 36-46% of the AD in feces. Peak plasma concentrations occurred within 45 minutes of dosing and plateaued within 6 hours post-dosing.
Toxicokinetics Mouse (B6C3F1) PMRA 2720107	B6C3F1 mice (♂ and ♀) receiving a single oral dose of 10 mg/kg bw of ^{14}C-amitraz both with and without preconditioning (dietary administration of 100 mg/kg bw/day and 400 mg/kg bw/day for two 3-week periods) excreted approximately 86% of the radioactivity within 24 hours, with 62% of the dose present in the urine. Urinary and fecal elimination rates did not differ with respect to sex or dietary pretreatment. Highest tissue radioactivity levels were seen in the liver, adrenal gland, and eyes with no obvious disparities noted with respect to preconditioned or non-preconditioned mice.

Study Type / Animal / PMRA #	Study Results
Toxicokinetics Rat (SD) PMRA 2720107	^{14}C-amitraz when administered as a single oral dose of 5 mg/kg bw to 2 ♂ SD rats was rapidly eliminated, with peak levels in the urine at 3-8 hours. Excretion occurred mainly via the urine (78% of the AD at 96 hours) with only limited fecal excretion (9% of the AD at 96 hours). Tissue radioactivity levels were highest in the liver. Metabolism studies with ♂ and ♀ SD rats receiving ^{14}C-amitraz as a single oral dose of 1, 10, 50, or 100 mg/kg bw indicated complete degradation to urinary metabolites and conjugates after 24 hours. Results further indicated that amitraz was rapidly hydrolyzed to BTS 27271 in the stomach, with further metabolism likely occurring by an enzymatic process that appeared to become saturated at high dose levels.
Toxicokinetics Dog (breed and sex unknown) PMRA 2720107	Results of testing with five dogs administered ^{14}C-amitraz as a single oral dose of 4 mg/kg bw by capsule demonstrated rapid absorption with peak blood levels occurring within 8 hours. Approximately 80% of the AD was excreted within 24 hours and 100% of the AD was excreted within 72 hours (80% urine, 20% feces). A single dog was given an oral dose of amitraz at 4 mg/kg bw approximately 15 minutes after feeding. Samples of the stomach contents were taken 15 minutes after dosing and at 30-minute intervals thereafter until the stomach was empty. BTS 27271 was detected in all samples with peak concentrations occurring at one hour post-dosing. Maximum concentrations of amitraz were found 15 minutes post-dosing. Thereafter, the residue level declined rapidly with time and was less than 0.1 ppm at one hour and 45 minutes post-dosing. Reaction products formed from ^{14}C-amitraz in canine gastric juice after 1 and 8 minutes revealed the presence of several breakdown products, namely BTS 23868 (44-72%), BTS 27271 (10-21%), and BTS 27919 (7-16%). Unchanged amitraz accounted for only a small % of the radioactivity (3-6%) after 1 and 8 minutes.
Toxicokinetics Baboon PMRA 2720107	A single oral dose of 10 mg/kg bw ^{14}C-amitraz when administered to baboons (1/sex) was excreted rapidly with 83% and 86% of the AD excreted within 72 hours in ♂ (58% urine, 25% feces) and in ♀ (76% urine, 10% feces), respectively. The highest tissue residue levels were in liver with relatively high levels also occurring in the eye.
Metabolism Various species PMRA 1936953	Trials conducted in the mouse, rat, dog, cat, calf, and cow indicated that conjugates of BTS 28369 were the major urinary metabolites which, upon hydrolysis, were converted to the free acid. Comparison of metabolism of ^{14}C-amitraz in the rat, mouse, baboon and human revealed that all urinary metabolites in these species were chromatographically indistinguishable. The data suggest that the following metabolites occurred in all species tested at levels of 1% to 6% each: BTS 24868, BTS 27919, BTS 28369, BTS 39098, BTS 31158, and BTS 27271. The metabolism/degradation of amitraz is fairly rapid and involves hydrolysis to BTS 27271 [N-(2,4-dimethylphenyl)-N`-methyl-formamidine] and BTS 27919 [2,4-dimethyl formanilide] with subsequent formation of the principal and terminal metabolite, BTS 28369 [4-amino-3-methyl benzoic acid].

Table 5 Toxicity Profile of Metabolites of Amitraz

[Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.]

Study Type / Animal / PMRA #	Study Results
BTS 28369 21-day oral (gavage) Rat (Boots-Wistar) PMRA 1244639	NOAEL not established as study was considered supplemental. 250 mg/kg bw/day: slight ↓ bw, ↓ BUN, ↓ urinary specific gravity (♂); ↑ rel. spleen wt (♀).
BTS 27271 90-day oral (capsule) Dog (Beagle) PMRA 1244637	NOAEL = 0.1 mg/kg bw/day 0.25 mg/kg bw/day: drowsiness or abnormal quietness often accompanied by sleep two hours post-dosing, ↓ body temperature one and two hours post-dosing. 1.0 mg/kg bw/day: ↓ heart rate one and two hours post-dosing.
BTS 28369 90-day oral (capsule) Dog (Beagle) PMRA 1244638	NOAEL = 100 mg/kg bw/day (highest dose tested)
BTS 24868 18-month oncogenicity (diet) Mouse (HaM/ICR) PMRA 2720761	NOAEL and LOAEL not established as study was considered supplemental. No evidence of oncogenicity.
BTS 24868 Two-year oncogenicity (diet) Rat (SD) PMRA 2720761	NOAEL and LOAEL not established as study was considered supplemental. Slight increase in pulmonary adenocarcinomas in ♂ (0/16, 0/20, 3/24). Equivocal evidence of oncogenicity.

Study Type / Animal / PMRA #	Study Results
Genotoxicity PMRA 1166802, 1166803, 1166804, 1166809, 1166814	BTS 27271 and BTS 27919 were negative in the microbial point mutation assay. BTS 24868 was negative for induction of micronuclei in mice (in vivo) and morphological transformation of mouse embryo fibroblasts (in vitro). Evidence of mutagenicity was demonstrated for BTS 24868 in a mammalian cell gene mutation assay using mouse lymphoma cells.

Table 6 Toxicology Reference Values for Use in Health Risk Assessment for Amitraz

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE
Dermal – all durations[2]	24-month dog oral (capsule); supported by results of the 90-day dog oral (capsule) study	NOAEL = 0.25 mg/kg bw/day CNS depression, ↓ body temperature and pulse rate.	300
Incidental oral – all durations	24-month dog oral (capsule); supported by results of the 90-day dog oral (capsule) study	NOAEL = 0.25 mg/kg bw/day CNS depression, ↓ body temperature and pulse rate.	300
Cancer	Overall, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.		

[1] MOE refers to a target MOE for residential assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation.

References

A. Studies Considered in the Chemistry Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1647186	1999, Amitraz Technical, Chemistry information , DACO: 2.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.1,2.13.2,2.13.3,2.13.4,2.2 CBI
1936869	2010, Product Identity, DACO: 2.1,2.2,2.3,2.4,2.5,2.6,2.7,2.8,2.9 CBI
1936871	1987, AMITRAZ: PHYSICAL AND CHEMICAL CHARACTERISTICS - COLOUR, PHYSICAL STATE AND ODOUR, DACO: 2.14.1,2.14.2,2.14.3 CBI
1936872	1987, THE DETERMINATION OF THE MELTING POINT OF AMITRAZ BY DIFFERENTIAL SCANNING CALORIMETRY (DSC)., DACO: 2.14.4 CBI
1936873	1987, THE DETERMINATION OF THE DENSITY OF AMITRAZ TECHNICAL., DACO: 2.14.6 CBI
1936874	1991, BTS 27919 (R000230): DETERMINATION OF THE pKa, DACO: 2.14.7 CBI
1936875	1989, AMITRAZ: SOLUBILITY IN ORGANIC SOLVENTS AT 25C, DACO: 2.14.8 CBI
1936876	1988, SOLUBILITY IN ORGANIC SOLVENTS - Addendum, DACO: 2.14.8 CBI
1936877	1987, DETERMINATION OF THE VAPOUR PRESSURE OF AMITRAZ, DACO: 2.14.9 CBI
1936879	1989, AMITRAZ: DETERMINATION OF THE pKa, DACO: 2.14.10 CBI
1936880	1990, AMITRAZ: DETERMINATION OF THE PARTITION COEFFICIENT BETWEEN N-OCTANOL AND WATER AT 25, DACO: 2.14.11 CBI
1936883	2008, UV Spectrophotometry of Amitraz Insecticide, DACO: 2.14.12 CBI
1936884	1989, AN ASSESSMENT OF THE SENSITIVITY OP TECHNICAL AMITRAZ TO METALS AND METAL IONS, DACO: 2.14.13 CBI
1936885	1993, THE DETERMINATION OF STORAGE STABILITY OF AMITRAZ TECHNICAL, DACO: 2.14.14 CBI
1954743	2010, Applicants Name and Manufacturers Name, DACO: 2.1,2.2 CBI
1954744	2009, Amitraz Technical (Alternate source) Product Properties - Group A, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.13.1,2.13.2 CBI
1954745	2010, Preliminary Analysis of Five Batches of TECHNICAL AMITRAZ, DACO: 2.13.3 CBI
2007057	Description of Starting Materials, DACO: 2.11.2 CBI
2007058	Detailed Production Process Description, DACO: 2.11.3 CBI
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2007061	Methodology/Validation, DACO: 2.13.1 CBI
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2020169	2011, Response to clarifications questions, DACO: 2.2 CBI

B. Studies Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2198090	2007, Acute Neurotoxicity Study of Amitraz in Rats, DACO: 4.5.12
2198091	2007, Ninety-Day Repeated Dose Oral Neurotoxicity Study of Amitraz by Dietary Administration in Rats, DACO: 4.5.12
2198092	2007, Homogeneity and Stability Test of Amitraz in Dosing Solution, DACO: 4.5.12
2198093	2006, Homogeneity and Stability of Amitraz in powder diet, DACO: 4.5.13
2404307	2014, An Oral (Gavage) Dose Range-Finding Toxicity Study of Amitraz in P-Generation Male and Female Rats and F1-Generation Pups - Final Report, DACO: 4.5.1,4.5.14
2668512	2016, Oral (Gavage) Extended One-Generation Reproduction Toxicity Study of Amitraz in Rats, DACO: 4.5.1,4.5.14
2668513	2016, Waiver Request for Developmental Toxicity in the Rabbit, DACO: 4.5.3
1149925	Multigeneration Feeding Test in Rats (T50) By M.M. Sutton Addendum Containing Table Of Pups Born Alive (Amitraz), DACO: 4.5.1
1166799	BTS 27419: Mutagenicity Testing Against Salmonella Typhimurium Strains TA1535, TA1537 and TA1538 in the Prsence and Absence of Liver Microsomes from Male and Female Mice, DACO: 4.5.4
1166800	Dominant Lethal Assay Of Amitraz in Female Mouse, DACO: 4.5.4
1166801	Dominant Lethal Assay Of Amitraz in Male Mouse, DACO: 4.5.4
1166802	Micronucleus Study In Mice Using BTS 24868, DACO: 4.5.4
1166803	Tech BTS 27271 Ames Bacterial Mutagenicity Test (Metabolite Of Amitraz), DACO: 4.5.4
1166804	Tech BTS 27919 Ames Bacterial Mutagenicity Test (Metabolite Of Amitraz), DACO: 4.5.4
1166806	Tech Amitraz: Ames Bacterial Mutagenicity Test, DACO: 4.5.4
1166807	Tech Amitraz: Induction Of Morphological Transformation in C3H10 T1\2 Cells, DACO: 4.5.4
1166808	Tech Amitraz: Unscheduled DNA Synthesis in Human Embryonic Cells, DACO: 4.5.4
1166809	Tech BTS 24868 (2,4-Xylidene): Mouse Lymphoma Mutation Assay, DACO: 4.5.4
1166810	Tech Amitraz: Mouse Lymphoma Mutation Assay, DACO: 4.5.4
1166814	Tech BTS 24868 (2,4-Xylidene): Induction of Morphological Transformation in C3H10 T1\2 Cells, DACO: 4.5.4
1166816	Amitraz 104 Week Tumorigenicity Study in Mice. Final Report. BTS 153/8262/A. DACO: 4.4.2
1166817	Amitraz 104 Week Tumorigenicity Study in Mice. Final Report. BTS 153/8262/A. Appendices., DACO: 4.4.2

1167708	Amitraz: Investigation of Effects on the Thymus Gland and Oestrous Cycle in Mice, DACO: 4.3.1
1167719	Amitraz: Effect of Amitraz on the Hepatic Mixed Function Oxidase System of Male and Female Mice Following Oral Administration. DACO: 4.5.9
1190339	Technical Amitraz: Range-Finding Study in the Pregnant Rat, DACO: 4.5.2
1190340	Technical Amitraz: Range-Finding Study in the Pregnant Rabbit, DACO: 4.5.3
1190341	Technical Amitraz: Teratogenicity Study in the Rat, DACO: 4.5.2
1190342	Technical Amitraz: Teratogenicity Study in the Rabbit, DACO: 4.5.3
1228854	Determination of Amitraz Concentrations in Methyl Cellulose Suspensions for Two Teratology Studies in the Rabbit (T278a), DACO: 4.5.2
1228856	Rabbit Teratogenicity Study (T279), DACO: 4.5.2
1228857	Rat Teratogenicity Study (T278), DACO: 4.5.2
1231956	1987, T294 Technical Amitraz: Assessment of Delayed Contact Hypersensitivity in the Guinea Pig, DACO: 4.2.6
1244605	BTS 27 419 – Interim Report After 52 Weeks of a 2 Year Chronic Toxicity Study in Rats, DACO: 4.4.1
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1244612	BTS 27 419 – Interim Report After 18 Months of a 2 Year Chronic Toxicity Study in Dogs, DACO: 4.4.1
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1244615	90 Day Toxicity Study in Rats, DACO: 4.7
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1244626	1972, 3 Month Feeding Study on Rats, DACO: 4.7
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1244635	BTS 27 419: 90 Day Chronic Toxicity Study in Mice, DACO: 4.7
1244637	1973, Oral Toxicity Study in Beagle Dogs, DACO: 4.7
1244638	1974, BTS 28 369: 90 Day Oral Toxicity Study in Dogs, DACO: 4.7
1244639	BTS 27 419 Metabolites: Chronic Oral Toxicity of BTS 28 369 To Rats, DACO: 4.7
1936905	1972, Acute Inhalation Toxicity to the Rat of BTS 27 419., DACO: 4.2.3
1936911	BTS 27419: Contact Sensitisation in the Guinea Pig., DACO: 4.2.6
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1936950	1988, Technical Amitraz Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro., DACO: 4.5.5
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Additional Information Considered

Published Information

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2720254	2015, M. Kanbur, Y. Silig, G. Eraslan, M. Karabacak, Z.S. Sarica, S. Sahin, The toxic effect of cypermethrin, amitraz and combinations of cypermethrin-amitraz in rats - Environmental Science and Pollution Research, Volume 25, Pages 5232 to 5242., DACO: 4.8

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C. Studies Considered in the Occupational Exposure Assessment

List of Studies/Information Submitted by Registrant

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1174806	CONCENTRATION OF AMITRAZ IN THE COLLAR (AND HAIR) WORN BY FEMALE BEAGLE DOGS, VIRBAC S.A., WIPE TEST

	COMPLEMENTARY INFORMATION, DATA TABLES, SUBN. # 90-0017 REGN. # 24496 (PREVENTIC COLLAR), DACO: 5.9

D. Additional Information Considered

Published Information

PMRA Document Number	Reference
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